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Diagnostic value of hepcidin in patients with sepsis and septic shock

Hepcidin with patients in sepsis and septic shock

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Abstract

Aim: Accelerating the diagnosis of sepsis patients and the ability to determine the severity of sepsis will speed up the treatment and thus decrease mortality and morbidity. Hepcidin is the regulator of iron metabolism, also an antimicrobial peptide and acute phase reactant, which is synthesized in hepatocytes. In the study, we aimed to determine the diagnostic value of this peptide, which is effective in sepsis by contributing to host defense, in patients with sepsis and septic shock.

Material and Methods: The study was carried out with patients who were admitted to the emergency department and were diagnosed with sepsis and healthy volunteers. Patients with a SOFA score of 2 and above were included in the study. The patient group was divided into sepsis and septic shock subgroups. Hepcidin, CRP, IL-6, TNF α, and leukocyte values were noted in the patient and control groups; also, SOFA scores were recorded. ROC analysis and AUC values were calculated for the determined data. P <0.05 value was considered statistically significant.

Results: A total of 86 cases were included in the study, as a healthy control group (n=23) and patient group [sepsis (n=32) and septic shock (n=31)]. When the relationship between biomarkers and binary study groups was evaluated, a statistically significant difference was observed between the control group and the patient group for hepcidin, leukocyte, TNF α, IL-6 and CRP values (p<0,05). While leukocyte, TNF-α, IL-6 and CRP values were significant in the binary comparison of control-sepsis groups, hepcidin values were not significant. However, no significance was found in other biomarkers in the comparison of sepsis-septic shock, while there was a statistically significant difference in hepcidin values (p=0,043). While sensitivity, specificity, PPV and NPV were calculated for hepcidin as 96,7%; 37,5% ; 60% and 92,31% respectively.

Discussion: The ability to determine the severity of the disease in the pre-intensive care period will speed up the treatment significantly and help to reduce mortality. According to the obtained findings in our study, we believe that hepcidin may be a useful biomarker in the diagnosis of septic shock and is correlated to the severity of the disease.

Keywords

Hepcidin, Sepsis, Septic Shock

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Introduction

Sepsis is a complex syndrome that develops in response to infection and has high mortality and morbidity rates [1]. Morbidity and mortality remain high despite the improved understanding of the pathophysiological pathways, pharmacological treatments, and intensive care in sepsis. Sepsis is a major public healthcare concern as it is one of the leading causes of mortality in the world and has a high incidence [2]. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) was published in 2016; the definitions of sepsis and septic shock were updated. However, to the best of my knowledge, there is no gold standard for diagnosis yet [3]. Therefore, diagnosis is challenging, and the initial treatment is delayed. Early detection of sepsis and its severity may facilitate early initiation of treatment and reduce mortality and morbidity in patients with a suspected diagnosis of sepsis.

Hepcidin, the hepatocyte-expressed antimicrobial peptide during infection, is an acute-phase reactant and the major regulator of systemic iron homeostasis that exhibits intrinsic antimicrobial activity [4]. Recent studies have shown the antimicrobial activity of hepcidin is due to the depletion of extracellular iron because of hepcidin induction. Hepcidin leads to a type of nutritional immunity that plays an important role against many extracellular bacterial infections [5]. All these features of hepcidin suggest that it is a significant marker in the diagnosis of sepsis, which is defined as an uncontrolled response to infection.

This study sought to determine the diagnostic value of hepcidin, which plays an important role in host defense, in patients with sepsis and septic shock and its relationship with other inflammatory markers.

Material and Methods

Study setting and design

This single-centered study was conducted in a Level 3 emergency department. The study was designed as a prospective cross-sectional study and approved by the local ethics committee (KAEK/2019.06.155). The study was conducted in accordance with the Declaration of Helsinki. The informed consent form was obtained from the patients and the volunteers.

Participant selection

This study included patients with sepsis who were admitted to the emergency department of the study center between August 2019 and May 2020; healthy volunteers constituted the control group. Patients admitted with suspected infection were assessed. SOFA scores were calculated for patients with suspected infection. Patients with SOFA scores of ≥2 were included in the study.

The patients were divided into three groups: sepsis, septic shock, and control. The sepsis group comprised patients with a mean arterial pressure (MAP) of ≥65 mmHg and lactate level of ≤2 mmol/dL after vasopressor support and adequate fluid resuscitation within the first hour, whereas the septic shock group comprised patients with an MAP of <65 mmHg and lactate level of >2 mmol/L after vasopressor therapy and adequate fluid resuscitation.

Patients aged <18 years, pregnant patients, and those diagnosed with hematologic malignancy or iron metabolism disorders were excluded from the sepsis and septic shock groups in this study. Healthy volunteers aged <18 years, pregnant volunteers, and volunteers with other known diseases and acute infection findings at hospitalization who had an iron metabolism-related disorder or received iron therapy were excluded from this study.

Measurements

Participants' age, sex, mean arterial pressures, GCS scores, leukocyte counts, SOFA scores were recorded at hospitalization. The levels of tumor necrosis factor (TNF-α), interleukin (IL)-6, and hepcidin levels were analyzed using enzyme-linked immunosorbent assay (ELISA).

ELISA

Synergy HTX (BioTek® Instruments, Inc., Winooski, VT, USA) device was used for ELISA. Sandwich ELISA was to quantitatively measure the levels of hepcidin, serum IL-6, and TNFα (Catalog Nos. SL1001 Hu, SL1761, and SL0868 Hu, Sunlong Biotech Co. Ltd., Hangzhou, China) following the manufacturer's instructions. Within- and between-group coefficients of variation of all three tests were <10% and <12%, respectively. Hemolytic and lipemic samples were excluded from the analysis.

Statistical analysis

Statistical analysis was performed for the comparison of the control and patient (sepsis and septic shock) groups as well as pairwise comparison of the three groups separately. The data were analyzed using the SPSS software version 26.0 (IBM Inc., New York, USA). The normal distribution of data was analyzed using the Kolmogorov–Smirnov and Shapiro-Wilk tests. Continuous variables with normal distribution were presented as means ± standard deviations and those with non-normal distribution as medians (Q1-Q3); categorical variables were presented as numbers (percentages). The comparison of two groups of non-normally distributed continuous variables was performed using the Mann–Whitney U test; the Pearson chi-square test was used to compare categorical data. Spearman's rank-order correlation analysis was used to determine the relationship among numeric variables. Correlated biomarkers were evaluated via receiver operating characteristic curve (ROC) curve analyses, and the area under the curve (AUC) values were determined. The cut-off point, sensitivity, specificity, and positive predictive values (PPV) and negative predictive values (NPV) for hepcidin, which was found to be the most informative biomarker, were determined and compared with the SOFA score. $p<0.05$ was considered statistically significant.

Ethical Approval

Ethics Committee approval for the study was obtained.

Results

This study included a total of 86 participants, including sepsis (n=32), septic shock (n=31), and control (n=23) groups. Women constituted 54.7% (n=47) and men 45.3% (n=39) of the cases in the study. The mean ages of the control, sepsis and septic shock groups were 60.73±13.34, 73.4±17.8, and 71.4±12.4, respectively. A significant difference was observed between the control and patient groups in terms of leukocyte count and TNF-α, IL-6, and CRP levels. Similarly, the difference between the control and sepsis groups was statistically significant (Table 1).

There was a statistically significant difference between

the control and patient groups in terms of the hepcidin level (p<0,042). However, no significant difference was noted between the control and sepsis groups (p<0,418). A significant difference was observed between the control and septic shock groups (p<0,01); thus, the group characteristics and hepcidin levels were analyzed by comparing the sepsis and septic shock groups (Table 1).

MAP, GCS, and SOFA score were significant between the sepsis and septic shock groups (p<0.05); however, the difference in terms of leukocyte count was not significant (p>0.05).

In the comparison of sepsis and septic shock groups, leukocyte count and CRP, TNF-α, IL-6 levels did not differ significantly (p=0.945, p=0.891, p=0.847, and p=0.192, respectively) between the groups, whereas hepcidin level did (p=0.043; Table 2).

When the correlations of the biomarkers within themselves as well as with the SOFA and were analyzed, a significantly positive correlation was detected between the hepcidin and IL-6 levels and SOFA score (p=0.001, p=0.003, respectively). The IL-6 level also has a positive correlation with the TNF-α level and SOFA score. No correlation was found among other biomarkers (p>0.05; Table 3).

In our study, hepcidin was identified as the most informative biomarker in the differentiation of sepsis from septic shock (AUC [95% confidence interval]: hepcidin, 0.648 [0.511-0.785]; IL-6, 0.596 [0.454-0.737]; TNF-α, 0.486 [0.339-0.633]; Figure

Table 1. Biomarker values of the study groups.

	1Control (n=23) Median [Q1-Q3]	2Sepsis (n=32) Median [Q1-Q3]	3Septic shock (n=31) Median [Q1-Q3]	P
Leukocyte (103/µl)	7,13 [5,29-8,6]	12,19 [8,43-19,77]	12,78 [6,01-23,38]	P1-2+3<0,01 P1-2<0,01 P1-3<0,01
TNF α (ng/L)	23,54 [22,71-25,19]	31,61 [26,50-33,56]	29,34 [25,49-38,69]	P1-2+3<0,01 P1-2<0,01 P1-3<0,01
IL-6 (ng/L)	5,33 [4,99-5,61]	6,09 [5,41-7,46]	6,28 [5,63-11,35]	P1-2+3<0,01 P1-2<0,01 P1-3<0,01
Hepcidin (ng/mL)	9,83 [9,3-10,2]	9,72 [9,22-11,75]	10,27 [9,58-14,26]	P1- 2+3<0,042 P1-2<0,418 P1-3<0,01
CRP (mg/L)	2,22 [1,08-3,2]	249,19 [123,26-319,20]	233,13 [142,17-313,5]	P1-2+3<0,01 P1-2<0,01 P1-3<0,01

TNFα: Tumor necrosis factor α, IL-6: Interleukin-6, CRP: C-reactive protein; Data are given as the median [IQR] for all biomarkers; Mann-Whitney U test was used for comparison of paired groups; p<0,05

Table 2. Comparison of clinical indicators, clinical scores and biomarkers in the sepsis and septic shock groups.

	Sepsis (n=32) Median [Q1-Q3]	Septic Shock (n=31) Median [Q1-Q3]	p
MAP (mmHg)	71,5 [60-96,75]	57 [47-67]	<0,0001*
GCS	14 [10,25-15]	10 [5-14]	0,003*
SOFA	5 [4-7,75]	10 [8-13]	<0,0001*
Leukocyte (103/µl)	12,19 [8,43-19,77]	12,78 [6,01-23,38]	0,945
TNF α (ng/L)	31,61 [26,50-33,56]	29,34 [25,49-38,69]	0,847
IL-6 (ng/L)	6,09 [5,41-7,46]	6,28 [5,63-11,35]	0,192
Hepcidin (ng/mL)	9,72 [9,22-11,75]	10,27 [9,58-14,26]	0,043*
CRP (mg/L)	249,19 [123,26-319,20]	233,13 [142,17-313,5]	0,891

MAP: Mean arterial pressure, GCS: Glasgow coma scale, SOFA: Sequential Organ Failure Assessment, APACHE II: Acute Physiology and Chronic Health Evaluation II, TNFα: Tumor necrosis factor α, IL-6: Interleukin-6, CRP: C-reactive protein, Mann-Whitney U test p<0,05

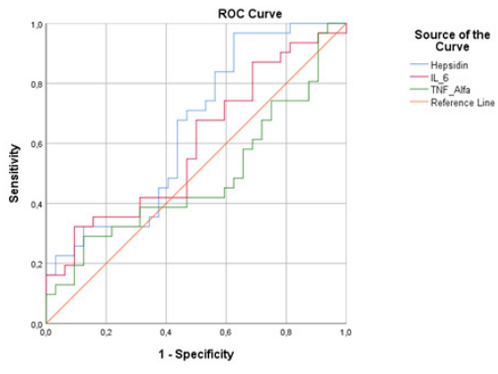

Figure 1. Representation of the diagnosis of septic shock with hepcidin, IL-6, TNF α by receiver operating curve (ROC) analysis.

Table 3. Correlation between biomarkers in sepsis and septic shock groups.

		Hepcidin (ng/mL)	Leukocyte (103/µl)	TNFa (ng/L)	IL-6 (ng/L)	CRP (mg/L)	SOFA
Hepcidin (ng/mL)	r		-0,008	0,191	0,396**	-0,163	0,369**
	p		0,948	0,133	0,001	0,201	0,003
Leukocyte (103/µl)	r	-0,008		0,099	-0,074	-0,072	-0,186
	p	0,948		0,438	0,564	0,575	0,145
TNFa (ng/L)	r	0,191	0,099		0,494**	-0,036	0,112
	p	0,133	0,438		<0,0001	0,78	0,38
IL-6 (ng/L)	r	0,396**	-0,074	0,494**		-0,1	0,358**
	p	0,001	0,564	<0,0001		0,436	0,004
CRP (mg/L)	r	-0,163	-0,072	-0,036	-0,1		-0,151
	p	0,201	0,575	0,78	0,436		0,237
SOFA	r	0,369**	-0,186	0,112	0,358**	-0,151	
	p	0,003	0,145	0,38	0,004	0,237	

TNFα: Tumor necrosis factor α, IL-6: Interleukin-6, CRP: C-reactive protein, SOFA: Sequential Organ Failure Assessment, APACHE II: Acute Physiology and Chronic Health Evaluation II, **p<0.01 ; r: Spearman correlation numbers

1). After identifying hepcidin as the most informative biomarker through ROC analysis, sensitivity, specificity, PPV, and NPV of hepcidin as the candidate diagnostic screening parameter were evaluated. The sensitivity was 96.7%, specificity 37.5%, PPV 60%, and NPV 92.31%.

Discussion

The aging of the world population and the increased incidence of related chronic diseases increase the number of patients with sepsis risk. Due to the emergence of the "sepsis" concept, several studies have been conducted to improve the diagnostic accuracy and treatment of sepsis; however, there is still no precise method that could become the gold standard, particularly from a diagnostic perspective. Reducing the time before the imitation of sepsis treatment in adult patients from 3–6 h to 1 h is required for an accurate and faster diagnosis, particularly in emergency departments, which are the first units that manage adult patients with sepsis [6].

Hepcidin is a relatively new peptide, which was first introduced by Krause et al. in 2000 [7]. The crucial role of hepcidin in the innate immune system is merely beginning to be understood. In recent years, the efficacy and importance of hepcidin in diagnosis have been investigated, particularly in children and newborns [4, 8]. However, there are very few studies on the diagnostic value of hepcidin in sepsis; furthermore, these studies were conducted on patients in the intensive care unit. Our study differs from these previous studies in that we focused on adult patients with sepsis who were in the pre-intensive care period of treatment.

In recent studies on the relationship between sepsis and hepcidin, the hepcidin level showed a significant difference between healthy controls and patients with sepsis regardless of the disease severity. Jiang et al. found that the hepcidin level was higher in the patient group than in the control group in their prospective study conducted on 198 patients and 20 healthy individuals [9]. Wu et al. investigated the diagnostic value of hepcidin in infants and found, regardless of disease severity, a significant difference in the hepcidin level between the sepsis and non-sepsis groups [8]. In our study, a significant difference was observed between the control and patient (sepsis+septic shock) groups in terms of the hepcidin level.

Yesilbas et al. determined the diagnostic role of hepcidin in children with sepsis and septic shock and found significantly higher hepcidin levels in both sepsis and septic shock groups than in healthy control and non-sepsis intensive care groups [4]. In our study, no significant difference was noted between the sepsis and control groups in terms of hepcidin levels, whereas a significant difference was observed between the septic shock and control groups. The hepcidin level was significantly higher in the septic shock group than in the sepsis group. The difference in the sepsis group in the abovementioned study might be explained by the fact that the study was conducted in intensive care unit patients, whereas our study used blood samples collected at emergency department registration.

In several previous studies, the hepcidin level has been reported to increase significantly with increasing disease severity [4, 9, 10]. One of the comprehensive studies is a prospective study conducted by Qui et al. who studied adult patients in the intensive care unit for 2 years. A total of 183 patients with (n=90) and without (n=93) sepsis were included in their study, and the sepsis group was divided into two subgroups as sepsis and septic shock, similar to our study. Their study demonstrated that the hepcidin level correlated with sepsis severity [10]. In our study, the hepcidin level was significantly higher in the septic shock group than in other groups. This might be related to the increased inflammation and antimicrobial efficacy of hepcidin as the disease severity increased.

Sepsis is a disease associated with high mortality. A meta-analysis published in 2020 reported that the 30-day mortality rate of septic shock was 34.7% and the 90-day mortality rate was 38.5% [11]. Several scoring systems such as APACHE II and SOFA were used to determine the severity of sepsis as well as other diseases in intensive care units. In addition, the SOFA score, which is also used currently for determining the prognosis, shows the severity of the disease, although it was created to identify the complications of severe patients and not as a mortality indicator [12,13]. In the last 20 years, several studies have reported inconsistent results regarding the superiority of scoring systems in revealing the disease severity and predicting short- or long-term mortality. Although no consensus has been reached yet regarding their superiority, the common view is that as sepsis severity increases, scores will increase in both scoring systems. In our study, we compared SOFA scores in the sepsis and septic shock groups and found high statistical significance in the septic shock group.

There was no significant difference in leukocyte count or CRP, TNF-α, and IL-6 levels between the sepsis and septic shock groups. The literature shows inconsistent results on this topic. Zhou et al. reported no significant difference in the CRP level between sepsis and septic shock groups in their study published in 2019 [14]. However, Zhang et al. found a significant difference between sepsis and septic shock groups in terms of the CRP level but not in leukocyte counts [15]. Although the general paradigm is that the TNF-α and IL-6 levels are associated with the disease severity, a study conducted by Rossi et al. in 2015, in which they calculated the daily IL-6 production in vivo, demonstrated that this production can range from a few micrograms per day to milligrams, indicating a wide variation. In addition, they demonstrated that CRP production was also inhibited, particularly in patients with low IL-6 expression [16]. Although infections may induce this production, we believe that this difference in our study might be because of the variations in IL-6 production observed in the study by Rossi et al. as well as because of the fact that the blood samples collected at emergency department registration were used in our study.

In the evaluation of the correlation of hepcidin with other biomarkers and scoring systems in our study, it was observed that hepcidin had a positive correlation with the IL-6 level as well as SOFA score; this finding was consistent with the findings of some previous studies [4, 5]. The comparison of the hepcidin level with the TNF-α and IL-6 levels was performed through ROC analysis. After identifying hepcidin as the most informative marker for predicting septic shock, the sensitivity, specificity, PPV, and NPV of hepcidin were calculated and compared with the SOFA scores. For the defined cutoff value, the sensitivity of hepcidin was 96.7%, specificity 37.5%, PPV 60%, and NPV

92.31%. We suggest that hepcidin is an important marker in the prediction of sepsis and septic shock due to the higher sensitivity and negative predicted value for the defined cut-off value compared to SOFA.

Limitation

There are some limitations of our study. The first is chronic diseases of patients in the sepsis and septic shock groups. We believe that some of the chronic diseases commonly noted in the age group of the patients included in our study may alter the levels of hepcidin and other biomarkers despite the fact that the patients with conditions that play a role in the production and consumption mechanism of hepcidin (pregnancy, hematologic malignancies, and iron metabolism disorder) were excluded from the study. In addition, considering the age of the healthy controls, there might have been undiagnosed chronic diseases in the control group. The small sample size of our study and single-centered study design represent the other limitations of our study.

Conclusion

Hepcidin may be a useful biomarker in the diagnosis of sepsis, and its level is associated with the severity of sepsis.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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